REMARKS

Claims 46-56, 58-64, and 66-109 are pending in the application. Claims 49, 50, 52-55, 58-60, 62-64, 67, and 69-103 were withdrawn from consideration. Examination of the remaining claims, 46-48, 51, 56, 61, 66, 68, and 104-109, is reported in the present Office Action. Each of the examined claims were objected to and were rejected under 35 U.S.C. §§ 112, second paragraph and 103(a). The objections and rejections are addressed below.

First, applicants note that the Examiner has stated that applicants' September 17, 2001 amendment erroneously requested a substitution at page 10, line 30 through page 13, line 10, while it appears that the amendment should have requested the substitution at page 10, line 24 through page 12, line 25. Applicants agree with the Examiner, and thus request that the amendment be made at page 10, line 24 through page 12, line 25.

Applicants also note that the Examiner has indicated that the executed declaration in this case does not properly make reference to the priority application, U.S. Serial No. 60/168,594. In reply, applicants enclose herewith a substitute declaration that includes a proper priority claim, and request that this priority claim be acknowledged.

The Examiner has maintained and made final the previously made Restriction Requirement. Applicants respectfully disagree with the Requirement. First, applicants note that the Office Action states that the Examiner acknowledges "applicant's election with traverse of Group I, claims 46-69, 93-98 and new claims 104-109 to the extent of methods of treating or preventing by administration with a peptide of SEQ ID NO:27..." Applicants respectfully request clarification of this statement. In particular, it appears from this statement that the sequence of SEQ ID NO:27 may be being read by the Examiner as a limitation of all of the

examined claims, not just those that include sequence identification numbers. Applicants respectfully submit that claims which do not include sequence identifiers should not be so limited, as that is not the way the claims were drafted. Further, applicants submit that having a sequence associated with a claim that involves the use of a protein or peptide is not required for a proper search for such a claim. For example, claim 46 specifies the use of an immunogenic fragment of an amyloid-β peptide, which certainly could be searched with respect to this fragment by use of the term "amyloid-β peptide" and its equivalents. If applicants have not misunderstood the Examiner's statement concerning the applicability of SEQ ID NO:27 to all of the claims, they respectfully request that the Examiner provide them with a specific reference to an authority which provides that it is acceptable for an Examiner to do what essentially amounts to a re-drafting of an applicants' claims to include a limitation that the applicants did not intend the claims to have.

Further regarding the Restriction Requirement, applicants note that the criteria for restriction in Markush claims (e.g., claim 61) are discussed in M.P.E.P. § 803.02. The requirements set forth in this section for maintaining the members of a Markush group in a single application are that the members must "(1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility." The members of the Markush groups of the present claims clearly meet these criteria. For example, in the case of the claims including multiple sequences, the peptide fragments having these sequences are all used as vaccine antigens to induce an immune response to β-amyloid, and thus share a common utility. In all being immunogenic fragments of Aβ peptides, they all share a substantial structural feature as well. The possibility that they may have some separate, independent uses is not relevant,

because the criteria cited above provide that they must share a common utility and a substantial structural feature, not all common utilities and all substantial structural features.

M.P.E.P. § 803.02 also states that "if the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions" (emphasis added; also see M.P.E.P. § 803.01). As is discussed above, the members of the Markush groups of the present claims are closely related, in being overlapping fragments of a single, short polypeptide. Moreover, the numbers of the members of the Markush groups are few. Thus, even if the members of the Markush groups were independent and distinct inventions, it would be incumbent upon the Examiner to search the full scope of the claims. Further, applicants submit that it is standard in the art to search a relatively longer sequence (e.g., a β-amyloid peptide sequence) and to obtain from the search hits that include shorter sequences (e.g., the sequences specified in claim 61) that have stretches of sequences that are identical to sequences within that of the larger sequence. Such a search could be done in the present case, to search the full scope of, e.g., claim 61, without undue burden. Applicants thus respectfully request that the Examiner reconsider the Restriction Requirement.

The Examiner has also required that corrected drawings be submitted in this case. Enclosed are formal drawings, including all of the changes required by the Office.

The Examiner further states that she has been unable to obtain access to one of applicants' co-pending applications, U.S. Serial No. 09/867,847, for evaluation of potential double patenting issues. Enclosed is a copy of the claims that are currently under examination in

the co-pending application, in the event that the Examiner has still not been able to access the application.

The objections and rejections are now addressed.

Claim Objections

Claims 46-48, 51, 56, 61, 66, 68, and 104-109 were objected to as reciting improper Markush groups. The Examiner supports this rejection by citing a passage from the M.P.E.P., § 803.02, which states "it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention," (citations omitted) and that "...unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." Applicants respectfully request that this objection be withdrawn.

First, applicants note that the only claims under examination that include Markush groups are claims 47, 48, 51, 56, and 61, and thus that this objection should not have even been considered with respect to claims 46, 66, 68, and 104-109.

Second, the elements in the claims that include Markush groups satisfy the criteria noted by the Examiner in this rejection. In particular, claims 47, 51, 56, and 61 each include within their Markush groups fragments of amyloid-β peptides. As is discussed above in reference to the Restriction Requirement, these peptides are all used to induce an immune response to amyloid-β peptide, and thus share a common utility, and are all amyloid-β fragments, and thus share a substantial structural feature that is essential to that utility. Thus, because the Markush groups of these claims meet the criteria for unity of invention in a Markush claim, as noted by the

Examiner, this objection should be withdrawn.

Regarding claims 48 and 56, applicants note that these claims includes two Markush groups that specify variable N-terminal and C-terminal substituents for the amyloid-β peptide fragments of claim 1. These substituents are chemical groups, e.g., alkyl groups, heterocyclic groups, acyl groups, alkoxy groups, and amino groups. Applicants note that it is standard for chemical patents to include claims that include Markush groups of chemical substituents that are far larger than these. It thus appears to be acceptable Patent Office practice to maintain such groups in chemical applications, and applicants respectfully submit that this standard should be applied in the present application as well. The elements of these Markush groups merely provide minor chemical modifications to the ends of the peptides, and surely the peptides themselves could be searched without these modifications (see above) with ease, and any hits analyzed for the presence of the short lists of substitutions in these Markush groups.

Claims 51, 56, 61, and 68 were also objected to for the use of the term "amyloid-β peptide" in a manner that the Examiner deems to be repugnant to the understanding of this term in the art. In particular, the Examiner states that those of skill in the art would recognize the term "amyloid-β peptide" as meaning a peptide having a specific sequence of 40-42 amino acids in length, and that the claims include within their scope sequences including deletions, insertions, or substitutions, as well as peptides of that vary in length from the accepted definition. While not necessarily agreeing with the Examiner's interpretation of the definition of amyloid-β peptide, in the interest of expediting prosecution, the present claims have been amended to reflect an understanding consistent with that of the Examiner. Thus, the claims formerly reciting "amyloid-β peptides" have now been amended to specify "immunogenic fragments of amyloid-β peptides"

instead. Applicants thus respectfully request that this objection be withdrawn.

Claim 51 was objected to under 37 C.F.R. § 1.75(c) as being in improper dependent form, for failing to limit further the subject matter of a previous claim. This objection is based on the assertion that the sequences encompassed by claim 51 contain fewer or different amino acids than what would be art-recognized as an amyloid-β peptide, which is specified in the claims from which claim 51 depends. This rejection can now be withdrawn, in light of the amendments discussed above, by which the claims now specify the use of immunogenic fragments of amyloid-β peptides.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 51, 56, 61, 66, and 68 were rejected under § 112, second paragraph as being indefinite in using the term "amyloid-β peptide" in a manner that, according to the Examiner, is repugnant to the meaning of this term in the art. As is discussed above, the claims have been amended to specify "immunogenic fragments of amyloid-β peptides," in place of "amyloid-β peptides." This rejection may therefore be withdrawn.

Claims 46-48, 51, 56, 61, 66, 68, and 104-109 were rejected under § 112, second paragraph as being indefinite in reciting the term "all D," which the Examiner states would be accepted in the art as meaning that every amino acid in the peptides are D amino acids. The Examiner thus concludes that the metes and bounds of the amino acids that are required to be D amino acids are indefinite. In the interest of expediting prosecution, applicants have amended the claims to specify that the peptides used in the claimed methods comprise at least 75% D amino acids. Support for this amendment can be found in applicants' definition of "all D"

peptides, which is on page 7, lines 32 and 33 of the specification.

Claims 104-109 were rejected under § 112, second paragraph as being indefinite for reciting the phrase "prevents and/or reduces." These claims have now been amended to specify "prevents or reduces" and, thus, applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 46-48, 51, 56, 61, 66, 68, and 104-109 were rejected under § 103(a) for obviousness over Shenk (WO 99/27944), Alberts (Molecular Biology of the Cell, 2nd Edn., Garland Publishing, 1989, p. 54), Tjernberg et al. (J. Biol. Chem. 271(15):8545-8548, 1996), Tjernberg et al. (J. Biol. Chem. 272(19):12601-12605, 1997), Soto et al. (Biochem. Biophys. Res. Comm. 226:672-680, 1996), Findeis et al. (U.S. Patent No. 5,854,204), Findeis et al. (U.S. Patent No. 5,985,242), Gross et al. (U.S. Patent No. 5,002,872), and Isowa et al. (U.S. Patent No. 4,116,768). This rejection is respectfully traversed.

This rejection is based on the assertion that Shenck suggests the use of amyloid-β peptides and fragments thereof to induce an immune response that reduces amyloid plaque formation; Tjernberg teaches peptides of the sequence of SEQ ID NO:27 and notes the benefit of using D peptides for inhibiting fibril formation, because of their being protease resistant; the Findeis patents teach D peptides of amyloid-β peptide (with optional terminal modifications) for inhibition of fibril formation; and Soto teaches the use of fragments of amyloid-β peptides, including D peptides, as being advantageous in being resistant to catabolism. The remaining references, Gross and Isowa, are cited for teaching C terminal modified, unsubstituted amino groups as protective groups for stabilizing peptide compounds *in vivo*.

The only reference that even mentions administration of amyloid-β peptide fragments for use as vaccine antigens is Schenk. But this reference does not mention a key feature of the present invention: the use of peptides including D amino acids. This difference is important because, as is discussed below, the present applicants have discovered that the use of such peptides provides significant advantages in vaccination that were not predictable over the prior art.

None of the other cited references provides any motivation to use D peptides in vaccination methods. Rather, the only cited references that suggest the use of D peptides do so for a completely different purpose: inhibiting fibril formation (see the Tjernberg, Findeis, and Soto references). The references suggest that such peptides may have improved stability, and this property is highlighted as being something which could improve the efficacy of the peptides in inhibiting fibril formation, because it is the peptides themselves that provide a therapeutic effect.

The benefit of D peptides in inhibiting fibril formation is not predictive of whether such peptides would be superior or even effective in being used as vaccine antigens, because in the case of vaccination, it is not the peptide itself that is a direct therapeutic agent. Rather, it is antibodies and other immune system components that are induced by the peptides that are therapeutic. In having these components induced, it was not predictable that having the peptides be more protease resistant (e.g., by including D amino acids) would be beneficial. Indeed, it could have been that including D amino acids actually interfered with proper processing and induction of immunity. This simply was not predictable. Thus, because the manner in which the D peptides are used in the present invention, as vaccine antigens, is completely different from

that of the references teaching D peptides, the improved effects of these peptides in the methods of the references are not at all predictive of their improved efficacy in a completely different context. The rejection under § 103(a) should therefore be withdrawn.

Further, as mentioned above, the present inventors have discovered that peptides including D amino acids are unexpectedly better than corresponding L peptides in inducing antibodies against amyloid-β peptides, as well as in decreasing Aβ levels in the brain. Experiments showing these results are described in the accompanying Declaration of Francine Gervais. As is stated in the Declaration, these experiments show that a D peptide including amino acids 10-22 of Aβ (BSA-(C)D10-22) induced a substantially higher level of antibodies in rabbits, as compared to a corresponding L peptide (BSA-(C)L10-22)(nearly 25,000 vs. undetectable). Similar results were obtained for another set of constructs including amino acids 10-22 of Aβ (KLH-(C)C10-22 vs. KLH-(C)L10-22). The experiments also show that a D peptide including amino acids 13-22 of Aβ (BSA-(C)D13-22) induced higher levels of antibodies in rabbits, as compared to a corresponding L peptide (BSA-(C)L13-22). The experiments in the Declaration further show that, overall, vaccination with a D peptide (D13-21-KLH) is more effective in decreasing the levels of Aβ40 and Aβ42 in the brains of a transgenic mouse model of Alzheimer's disease, as compared to a corresponding L peptide (L13-21-KLH), and that the D peptide is also more effective at increasing plasma levels of Aβ in the immunized mice, as compared to the corresponding L peptide.

The unexpected results of the experiments described in the Declaration, showing the superiority of D peptides over L peptides in inducing antibodies against Aβ, as well as in decreasing Aβ levels in the brain, certainly were not predictable from the prior art. Moreover, as

is discussed in the Declaration, applicants' observations of increased Aβ plasma levels in patients treated with D peptides as compared to L peptides were surprising, as prior studies employing L peptide immunogens had not reported detection of increased Aβ plasma levels. Also as is stated in the Declaration, the increased Aβ plasma levels obtained using D peptides is indicative of a significant therapeutic benefit, as the increased amount of Aβ present in the plasma is material that is not in the brain, where its presence is associated with the etiology of Alzheimer's Disease. This is a substantial development in this field, which certainly would not have been predictable based on the prior art.

Thus, because it was not predictable based on the cited references that D peptides would be effective vaccine antigens, not to mention superior vaccine antigens, having previously unknown beneficial effects (e.g., decreased Aβ in the brain and increased Aβ in the plasma), as applicants discovered, the rejection of the present claims for obviousness should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: July 2, 2003

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Version of Amendment with Markings to Show Changes Made

46. (Twice Amended) A method for preventing or [and/or] treating an amyloid-related disease in a subject, comprising: administering to the subject an antigenic amount of an immunogenic fragment of an [all-D] amyloid-β peptide, wherein said [all-D amyloid β peptide induces an immune response by said subject against said amyloid-β peptide] fragment comprises at least 75% D amino acids.

47. (Twice Amended) The method of claim 46, wherein said immunogenic fragment of an [all-D] amyloid-β peptide comprises [interacts with] at least one region of an amyloid protein, said region being selected from the group consisting of: C-terminal region, β sheet region, GAG-binding site region, cellular adherence region, immunogenic fragments thereof, protein conjugates thereof, immunogenic derivative peptides thereof, immunogenic peptides thereof, and immunogenic peptidomimetics thereof.

48. (Twice Amended) The method of claim 46, wherein said immunogenic fragment of an [all-D] amyloid-β peptide further comprises:

an N-terminal substituent selected from the group consisting of:

hydrogen;

lower alkyl group consisting of acyclic or cyclic having 1 to 8 carbon atoms;

aromatic group;

heterocyclic group; and

acyl group; and

a C-terminal substituent selected from the group consisting of hydroxy, alkoxy, aryloxy, unsubstituted and substituted amino groups.

51. (Twice Amended) The method of claim 48, wherein said immunogenic fragment of an [all-D] amyloid-β peptide is selected from the group consisting of SEQ ID NOs:1-48.

56. (Twice Amended) A method for preventing or [and/or] treating an amyloid-related disease in a subject, comprising administering to the subject an antigenic amount of a peptide having Formula I:

R' -(P)-R" (I)

wherein

P is an immunogenic fragment of an [all-D] amyloid-β peptide selected from the group consisting of: Aβ(1-42, all-D), C-terminal region, β sheet region, GAG-binding site region, cellular adherence region, immunogenic fragments thereof, protein conjugates thereof, immunogenic derivative peptides thereof, immunogenic peptides thereof, and immunogenic peptidomimetics thereof;

R' is an N-terminal substituent selected from the group consisting of:

hydrogen;

lower alkyl group consisting of acyclic or cyclic having 1 to 8 carbon atoms;

aromatic group;

heterocyclic group; and

acyl group; and

R" is a C-terminal substituent selected from the group consisting of hydroxy group, alkoxy group, aryloxy group, unsubstituted group, and substituted amino group, wherein said immunogenic fragment of an [all-D] amyloid-β peptide induces an immune response by said subject against said immunogenic fragment [all-D amyloid-β peptide].

61. (Twice Amended) The method of claim 56, wherein said immunogenic fragment of an [all-D] amyloid-β peptide is selected from the group consisting of SEQ ID NOs:1-48.

104. (Amended) The method of claim 46, wherein said immune response prevents or [and/or] reduces amyloid fibril formation.

105. (Amended) The method of claim 46, wherein said immune response prevents or [and/or] reduces amyloid-induced neurodegeneration.

106. (Amended) The method of claim 46, wherein said immune response prevents or [and/or] reduces amyloid-induced cellular toxicity.

107. (Amended) The method of claim 56, wherein said immune response prevents or [and/or] reduces amyloid fibril formation.

108. (Amended) The method of claim 56, wherein said immune response prevents or [and/or] reduces amyloid-induced neurodegeneration.

109. (Amended) The method of claim 56, wherein said immune response prevents or [and/or] reduces amyloid-induced cellular toxicity.

Claims under examination in U.S. Serial No. 09/867,847

1. A method for preventing or treating an amyloid-related disease in a subject, comprising: administering to the subject an antigenic amount of an all-D peptide, wherein said all-D peptide elicits the production of antibodies against said all-D peptide and induces an immune response by said subject, thereby preventing or reducing amyloid-induced neurodegeneration or amyloid fibril formation.

2. A method for preventing or treating an amyloid-related disease in a subject, comprising: administering to the subject an antigenic amount of an all-D peptide, wherein said all-D peptide interacts with an amyloid protein, elicits the production of antibodies against said all-D peptide, and induces an immune response by said subject, thereby preventing or reducing amyloid-induced cellular toxicity or amyloid fibril formation.

3. The method of claim 1, wherein said all-D peptide comprises a peptide of at least one region of an amyloid fibril or an amyloid protein, said region being selected from the group consisting of: Aβ(1-42), C-terminal region, β sheet region, GAG-binding site region, cellular adherence region, immunogenic fragments thereof, protein conjugates thereof, immunogenic derivative peptides thereof, immunogenic peptides thereof, and immunogenic peptidomimetics thereof.

4. The method of claim 3, wherein said all-D peptide further comprises:

(a) an N-terminal substituent selected from the group consisting of:

hydrogen;

lower alkyl group consisting of acyclic or cyclic having 1 to 8 carbon atoms;

aromatic group;

heterocyclic group; and

acyl group; and

(b) a C-terminal substituent selected from the group consisting of hydroxy, alkoxy, aryloxy, unsubstituted and substituted amino groups.

5. The method of claim 4, wherein said alkyl or aromatic group is further substituted with a group selected from the group consisting of halide, hydroxyl, alkoxyl, aryloxyl, hydroxycarbonyl, alkoxylcarbonyl, aryloxycarbonyl, carbamyl, unsubstituted amino, substituted amino, sulfo, alkyloxysulfonyl, phosphono and alkoxyphosphonyl groups.

6. The method of claim 4, wherein said all-D peptide further comprises an acid functional group, or a pharmaceutically acceptable salt or ester form thereof.

7. The method of claim 4, wherein said all-D peptide further comprises a base functional group, or a pharmaceutically acceptable salt form thereof.

8. The method of claim 3, wherein said all-D peptide comprises SEQ ID NO:15.

12. A method for preventing or treating an amyloid-related disease in a subject, comprising:

administering to the subject an antigenic amount of a peptide having Formula I:

R'—(P)—R" (I)

wherein

P is an all-D peptide of an amyloid fibril or an amyloid protein selected from the group consisting of: Aβ(1-42), C-terminal region, β sheet region, GAG-binding site region, cellular adherence region, immunogenic fragments thereof, protein conjugates thereof, immunogenic derivative peptides thereof, immunogenic peptides thereof, and immunogenic peptidomimetics thereof;

R' is an N-terminal substituent selected from the group consisting of:

hydrogen;

lower alkyl group consisting of acyclic or cyclic having 1 to 8 carbon atoms;

aromatic group;

heterocyclic group; and

acyl group; and

R" is a C-terminal substituent selected from the group consisting of hydroxy group, alkoxy group, aryloxy group, unsubstituted group, and substituted amino group.

13. The method of claim 12, wherein said all-D peptide elicits the production of antibodies against said all-D peptide, and induces an immune response by said subject, thereby preventing or reducing amyloid-induced neurodegeneration or amyloid fibril formation.

14. The method of claim 12, wherein said alkyl or aromatic group is further substituted with a group selected from the group consisting of halide, hydroxyl, alkoxyl, aryloxyl, hydroxycarbonyl, alkoxylcarbonyl, aryloxycarbonyl, carbamyl, unsubstituted amino, substituted amino, sulfo, alkyloxysulfonyl, phosphono and alkoxyphosphonyl groups.

15. The method of claim 12, wherein said all-D peptide further comprises an acid functional group, or a pharmaceutically acceptable salt or ester form thereof.

16. The method of claim 12, wherein said all-D peptide further comprises a base functional group, or pharmaceutically acceptable salt form thereof.

17. The method of claim 12, wherein said all-D peptide comprises SEQ ID NO:15.